



## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>S-30287/A</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 98/ 07792</b>	International filing date (day/month/year) <b>01/12/1998</b>	(Earliest) Priority Date (day/month/year) <b>03/12/1997</b>
Applicant <b>NOVARTIS AG et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

09/554,941  
Exhibit A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/07792

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/82 C12N15/52 C12N15/53 C12N9/00 C12N9/02  
 C12N5/10 G01N33/50 A01H5/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 10083 A (CIBA GEIGY AG) 4 April 1996 page 3,6; example 22 ---	1,2,7, 13,15-17
X	EP 0 497 366 A (DONEGANI GUIDO IST) 5 August 1992 pages 5,6-15,16; page 18, line 43-50; claims ---	1,2,8, 13,15-17
Y	WO 96 16173 A (UNIV LEEDS ; ATKINSON HOWARD JOHN (GB); MCPHERSON MICHAEL JOHN (GB)) 30 May 1996 pages 1,3,4,5,; page 6, line 16-20; page 11,22-30; claims 27-38; Table 3 --- -/--	1-4,7, 12-17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

25 March 1999

Date of mailing of the international search report

13/04/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Holtorf, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 13810 A (UNIV MELBOURNE ; ANDERSON MARILYN ANNE (AU); ATKINSON ANGELA HILARY) 23 June 1994	1-3,7, 13-17
Y	see page 4	1-4,6,7, 12-17
Y	--- WO 97 20057 A (NICKERSON BIOCEM LTD ; ATKINSON HOWARD JOHN (GB); LILLEY CATHERINE) 5 June 1997 page 7,8,11; example 3,4,5; claims	6
A	--- WO 92 15690 A (NICKERSON BIOCEM LTD) 17 September 1992 pages 6,7,9,10; examples 1,6	1-17
A	--- LILLEY, C.J., ET AL. : "characterization of intestinally active proteinases of cyst nematodes" PARASITOLOGY, vol. 113, no. Pt4, October 1996, pages 415-425, XP002097967 abstract; page 416,417,420,423, left column	1-17
A	--- URWIN P E ET AL: "RESISTANCE TO BOTH CYST AND ROOT-KNOT NEMATODES CONFERRED BY TRANSGENIC ARABIDOPSIS EXPRESSING A MODIFIED PLANT CYSTATIN" PLANT JOURNAL, vol. 12, no. 2, 1997, pages 455-461, XP000198746 page 459, right column	1-17
P,X	--- URWIN, P.E., ET AL.: "enhanced transgenic plant resistance to nematodes by dual proteinase inhibitor constructs" PLANTA, vol. 204, April 1998, pages 472-479, XP002097968 see the whole document -----	1-10,12, 13,15-17

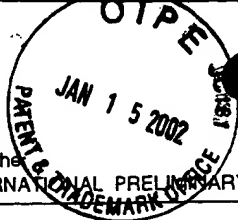
## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/07792

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9610083. A	04-04-1996	US 5849870 A	15-12-1998
		AU 692934 B	18-06-1998
		AU 3743395 A	19-04-1996
		BG 101384 A	31-10-1997
		BR 9509099 A	30-09-1997
		CA 2199049 A	04-04-1996
		CN 1160420 A	24-09-1997
		EP 0792363 A	03-09-1997
		HU 77449 A	28-04-1998
		JP 10506532 T	30-06-1998
		US 5872212 A	16-02-1999
		US 5770696 A	23-06-1998
		US 5840868 A	24-11-1998
		US 5866326 A	02-02-1999
		US 5877012 A	02-03-1998
		ZA 9508121 A	29-04-1996
EP 0497366 A	05-08-1992	AU 648140 B	14-04-1994
		AU 1065092 A	06-08-1992
		CA 2060455 A	02-08-1992
		JP 5294995 A	09-11-1993
		US 5519115 A	21-05-1996
WO 9616173 A	30-05-1996	AU 3877095 A	17-06-1996
		CA 2205356 A	30-05-1996
		EP 0793722 A	10-09-1997
		JP 10510146 T	06-10-1998
WO 9413810 A	23-06-1994	AU 680855 B	14-08-1997
		AU 5689194 A	04-07-1994
		CA 2151933 A	23-06-1994
		EP 0674712 A	04-10-1995
		JP 8506482 T	16-07-1996
		NZ 258824 A	24-11-1997
WO 9720057 A	05-06-1997	AU 7702496 A	19-06-1997
		CA 2238943 A	05-06-1997
		EP 0871752 A	21-10-1998
WO 9215690 A	17-09-1992	AT 160175 T	15-11-1997
		AU 665530 B	11-01-1996
		AU 1353192 A	06-10-1992
		CA 2107234 A	06-09-1992
		DE 69223080 D	18-12-1997
		DE 69223080 T	25-06-1998
		EP 0502730 A	09-09-1992
		ES 2111041 T	01-03-1998
		GR 3026133 T	29-05-1998
		US 5494813 A	27-02-1996



PATENT COOPERATION TREATY

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT 1c

WRITTEN OPINION

(PCT Rule 66)

To:

Becker, Konrad  
NOVARTIS AG  
Corporate Intellectual Property  
Patent & Trademark Department  
CH-4002 Basel  
SUISSE

P + TM Dept.

18. Okt. 1999

APPL M/D F/L PS/43

Kopien:

Date of mailing  
(day/month/year)

12. 10. 99

Applicant's or agent's file reference

S-30287/A

REPLY DUE

within 3 month(s)  
from the above date of mailing

International application No.

PCT/EP98/07792

International filing date (day/month/year)

01/12/1998

Priority date (day/month/year)

03/12/1997

International Patent Classification (IPC) or both national classification and IPC

C12N15/82

Applicant

NOVARTIS AG et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion  
II ☐ Priority  
III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  
IV ☐ Lack of unity of invention  
V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement  
VI ☐ Certain document cited  
VII ☐ Certain defects in the international application  
VIII ☒ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 03/04/2000.

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Merlos-Lange, A.M.

Formalities officer (incl. extension of time limits)

Vullo, C

Telephone No. +49 89 2399 8061



09/554.941  
Exhibit B

## WRITTEN OPINION

International application No. PCT/EP98/07792

### I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*).

#### Description, pages:

1-32 as originally filed

#### Claims, No.:

1-17 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

### V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### 1. Statement

Novelty (N)	Claims	see sep. sheet
Inventive step (IS)	Claims	see sep. sheet
Industrial applicability (IA)	Claims	

2. Citations and explanations  
see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

- 1.1 With respect to document WO 96/10083, claims 1, 2, 7, 13 and 15-17 appear not to conform with the requirements of Art. 33(2), (3) PCT. Said document describes the recombinant production of fusion proteins optionally linked by a linker region for the purpose of protecting plants against insect pests (see pages 3 and 4, 6 and 7, Example 22 and part of the claims).

Alternatively, with respect to documents EP-0 497 366 and WO 94/13810, it would appear that claims 1, 2, 3, 6, 7, 8 and 12-17 do not refer to novel and inventive matter.

WO 94/13810 discloses the construction of proteinase inhibitor fusion proteins linked via a protease sensitive linker so that upon expression in a plant transformed with said construct, the plant proteinases cleave the fusion molecule. The fusion protein should increase, enhance or facilitate in plants, the resistance to insects or other pathogens.

Document EP-A-0 497 366 describes the construction of so-called "bridged" oligopeptides to protect plants against microbial pathogens (see page 5, last paragraph, page 7, 16-21).

At present, the above cited claims are too generally drafted and lack any particular features which would impart novelty and/or inventiveness to the subject-matter claimed.

- 1.2 It is further noted that document WO 96/16173 refers to the development of modified and thus more effective proteinase inhibitors such as Oc-IdeltaD86 to make plants nematode-resistant. The use of such proteinase inhibitors in the method as claimed in claims 1-4, 7 and 12-17 therefore appears obvious and thus not inventive (Art. 33(3) PCT).

- 2). Having regard to claim 5, it is unclear whether the used proteinase inhibitor CpTI is commonly known and made available to the public (Art. 5 and 6 PCT).

The expression "preferentially" used in claim 6 raises unclarity whether the promoter is root-specific or not.



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>S-30287/A</b>	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/EP98/07792</b>	International filing date (day/month/year) <b>01/12/1998</b>	Priority date (day/month/year) <b>03/12/1997</b>	
International Patent Classification (IPC) or national classification and IPC <b>C12N15/82</b>			
Applicant <b>NOVARTIS AG et al.</b>			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>10/06/1999</b>	Date of completion of this report <b>27. 03. 00</b>
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>A. M. Merlos</b>  Telephone No. +49 89 2399 8559 

09/554.941  
Exhibit C

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP98/07792

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-32 as originally filed

**Claims, No.:**

1-17 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	4, 5, 6, 9-11
	No:	Claims	1, 2, 3, 7, 8, 12-17
Inventive step (IS)	Yes:	Claims	9-11
	No:	Claims	1-8, 12-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP98/07792

---

**2. Citations and explanations**

**see separate sheet**

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

**and / or**

**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/EP98/07792

- 1.1 With respect to document WO 96/10083, claims 1, 2, 7, 13 and 15-17 appear not to conform with the requirements of Art. 33(2), (3) PCT. Said document describes the recombinant production of fusion proteins optionally linked by a linker region for the purpose of protecting plants against insect pests (see pages 3 and 4, 6 and 7, in particular Example 22 and part of the claims).  
Alternatively, with respect to documents EP-0 497 366 and WO 94/13810, it would appear that claims 1, 2, 3, 6, 7, 8 and 12-17 do not refer to novel and/or inventive subject-matter.  
WO 94/13810 discloses the construction of proteinase inhibitor fusion proteins linked via a protease sensitive linker so that upon expression in a plant transformed with said construct, the plant proteinases cleave the fusion molecule. The fusion protein should increase, enhance or facilitate in plants, the resistance to insects or other pathogens (see page 8, line 15 to page 12, line 31, claims). Document EP-A-0 497 366 describes the construction of so-called "bridged" oligopeptides to protect plants against microbial pathogens (see page 5, last paragraph, pages 7 and 16-21).  
At present, claims 1-3, 6-8, and 12-17 are too generally drafted and lack any particular features which would render the matter claimed clearly novel and/or inventive with respect to the prior art.
- 1.2 It is further noted that document WO 96/16173 refers to the development of modified and/or hybrid proteinase inhibitors which are more effective in making plants nematode-resistant. The use of such hybrid proteinase inhibitors in the method as claimed in claims 1-4, 7, 12 and 17, the fusion proteins and transgenic plants expressing them and the corresponding DNA molecules encoding these hybrids (claims 13-16) therefore appear obvious. Said claims are therefore regarded to lack an inventive aspect according to (Art. 33(3) PCT).  
This is also true for claim 5 wherein the method particularly refers to CpTI, insofar as the cowpea trypsin inhibitor (CpTI) was already known to have anti-nematode activity (see WO92/15690).
- 2). The expression "preferentially" used in claim 6 raises unclarity whether the claim is limited to a root-specific promoter or not.
- 3). In case of an unvalid priority of 03.12.1997, intermediate document "Urwin et al., Planta, vol. 204, April 1998, pages 472-479" may become relevant when the

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/EP98/07792

application enters the european phase.